Drug Monograph

A - Drug Name

vinCRIStine

SYNONYM(S): LCR; leurocristine; VCR

COMMON TRADE NAME(S): Oncovin® (multiple brands available)

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B - Mechanism of Action and Pharmacokinetics

The vinca alkaloids have become clinically useful since the discovery of their antitumour properties in 1959. Vincristine binds reversibly to spindle proteins in S phase. Inhibition of RNA synthesis has also been noted. Vincristine has been shown to arrest cells in metaphase.

Absorption	Not absorbed orally	
Distribution	Rapid and extensive reversible tissue binding	
	Cross blood brain barrier?	Minimal
	PPB	75 %
Metabolism	Metabolized in liver by the CYP 3A4 family of P450 isoenzymes	
	Active metabolites	no information found
	Inactive metabolites	no information found
Elimination	Disposition described by a three-compartment model; 30% of the dose is excreted into bile and feces.	
	Urine	10-20%
	Half-life	T ½ α : 5 min

T ½ ß : 2.3 hours

T ½ (gamma) : 85 hours

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C - Indications and Status

Health Canada Approvals:

- Acute leukemias (acute lymphoblastic leukemia, acute myeloid leukemia)
- Breast cancer
- Sarcomas (soft tissue, bony tissue, specialized structures)
- Hodgkin's disease
- Non-Hodgkin's lymphoma
- Small cell lung cancer
- Cervical Cancer
- Colorectal cancer
- Wilm's tumour
- Melanoma

Other Uses:

- Other hematological cancers (chronic lymphocytic leukemia, myeloma)
- Gastrointestinal cancers (gastroesophageal, hepatobiliary, pancreatic, neuroendocrine tumours)
- Genitourinary cancers (adrenal, prostate)
- Gynecological cancers (endometrial, ovarian, GTD)
- Thymoma
- Brain tumours

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: Vesicant

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (rare)	E
Cardiovascular	Hypertension (rare, autonomic)	E
	Hypotension (rare, autonomic)	E
Dermatological	Alopecia (up to 50%)	E
	Rash (occasional)	I E
Gastrointestinal	Abdominal pain	E
	Anorexia, weight loss	E
	Constipation (neuropathy)	E
	Diarrhea	E
	GI perforation	E
	Mucositis	E
	Nausea, vomiting (mild)	I
Hematological	Myelosuppression (mild)	E
Hypersensitivity	Hypersensitivity (rare)	I
Injection site	Phlebitis (chemical)	I E
Metabolic / Endocrine	SIADH (rare, central neurotoxicity)	E
	Tumor lysis syndrome	I
Musculoskeletal	Musculoskeletal pain (may be severe)	E
Neoplastic	Secondary malignancy (in combination)	D
Nervous System	Autonomic neuropathy (paralytic ileus)	E
	Cranial neuropathy (rare; diplopia, transient blindness, optic atrophy)	E
	Headache	E
	Insomnia (rare)	E
	Peripheral neuropathy (common)	I E D
	Seizure (rare)	I
	Vertigo (rare)	E
Reproductive and breast disorders	Infertility	E
Respiratory	Bronchospasm (acute, rare)	I
Urinary	Urinary retention (autonomic neuropathy; may be severe)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common adverse effects are alopecia and neurotoxicity. Myelosuppression is minimal.

Hyperuricemia during periods of active cell lysis can be minimized with allopurinol and hydration. However, fluid restriction may be required for a patient showing signs of SIADH. In hospitalized patients the urine may be alkalinized, by addition of sodium bicarbonate to the IV fluids.

The **tissue necrosis** that happens with **extravasation** may happen days to weeks after the treatment. Patents must be observed for delayed reactions and prior injection sites carefully inspected.

Neurotoxicity with the vinca alkaloids is dose-limiting, qualitatively similar but quantitatively different (vincristine >vinblastine>vinorelbine). It is dose- and exposure-related, with increased toxicity in prolonged infusion. Previous neurotoxicity or neurological disorders may result in decreased tolerance and increased sensitivity. Neurotoxicity is generally reversible, but recovery may be slow.

The most frequent manifestation of nervous system toxicity is **peripheral neuropathy**; the earliest indication of which is the depression of the Achilles reflex. Later loss of other deep tendon reflexes occurs and is accompanied by peripheral paresthesias, pain and tingling. If therapy is prolonged or high doses are administered, wrist and foot drop, ataxia, a slapping gait and difficulty in walking may occur. Young children may refuse to walk due to extremity pain.

Cranial nerve neuropathy may lead to vocal cord paresis or paralysis (hoarseness, weak voice), ocular motor nerve dysfunction (ptosis, strabismus), bilateral facial nerve palsies, or jaw pain. Severe jaw pain can occur within a few hours of the first dose of vincristine. Cranial nerve toxicities tend to be bilateral and reversible when treatment with vincristine is discontinued.

Autonomic neuropathy is manifested as constipation (which can be severe), abdominal pain, urinary retention and paralytic ileus. Laxatives or stool softeners should be given routinely to prevent constipation. These symptoms resolve with time and may not occur with subsequent treatment. Urinary retention may occur in older patients with obstructive uropathy. If bladder atony occurs, vincristine should be held until symptoms resolve.

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E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. **SPECIAL LABELLING IS REQUIRED.** (see Administration Guidelines)

Adults:

Intravenous: 1.4 mg/m^2 weekly
Intravenous: 1 to 1.4 mg/m^2 q2-3 weeks (maximum dose of 2 mg used in some regimens)

Dose capping
Due to concerns of neurotoxicity, the ASCO guideline recommends vincristine to be capped at a maximum dose of 2 mg when used as part of the CHOP and CVP regimens. It would be prudent to question any dose of vincristine >3 mg or more frequent administration than once a week.

Dosage with Toxicity:

Toxicity / Worst counts in cycle	Action*
Febrile neutropenia, thrombocytopenic bleeding or grade 4 ANC ≥ 7 days	Hold; No dose adjustment required
Neurotoxicity • Areflexia only • Abnormal buttoning, writing • Moderate motor neuropathy (± cranial) • Severe motor neuropathy	 • 100% • 67% • Hold until recovery then reduce dose by 50% • Omit
Respiratory symptoms (e.g. bronchospasm, pneumonitis)	Discontinue
Grade 3 other related non-hematological/organ toxicity	Hold
Grade 4 other related non-hematological/organ toxicity	Discontinue
*Do not re-treat unless ANC 1.5 x 10^9L (or defined by protocol), platelets ≥ 100 x 10^9L and other toxicities have recovered to ≤ grade 2 or indicated in table above.	

Dosage with Hepatic Impairment:

Bilirubin	% usual dose
> 1 – 2.5 x ULN	50%
> 2.5 x ULN	25%

Dosage with Renal Impairment:

No adjustment required

Dosage in the elderly:

Older patients may have more neurotoxicity.

Children:

Refer to regimen being used. Infants are especially susceptible to neurotoxicity and doses should be based on body weight rather than surface area. Doses may be gradually increased as tolerated. Infants are also more susceptible to ileus, SIADH and hematological toxicities from vincristine.

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F - Administration Guidelines

FOR INTRAVENOUS USE ONLY. Vincristine is lethal if given intrathecally. No successful antidotes have been described. **Syringes containing this product should be labelled "WARNING – FOR INTRAVENOUS USE ONLY. FATAL if given by other routes."**

- Direct IV push not recommended, due to risk of inadvertent intrathecal administration.
- For intermittent IV use, may mix in small volume minibag (ie. 50mL NS or D5W for adults).
- Infuse IV via gravity. Infusion pumps should not be used peripherally, since they deliver infusions at higher pressures and may continue to infuse when extravasation occurs.

- During the infusion, suggest nurse to remain present with the patient to observe the IV site for extravasation.

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G - Special Precautions

Other:

Contraindicated in patients with the demyelinating form of Charcot-Marie-Tooth Syndrome, childhood polio or with hypersensitivity to vinca alkaloids. Intrathecal administration is **absolutely contraindicated**. Vincristine should not be given to patients who are receiving radiation that includes liver portals. Use with caution with other neuromuscular disorders, neurotoxic/ototoxic drugs, in leukopenia, complicating infection, or and in patients with Guillain-Barre Syndrome.

Vincristine is potentially **fetotoxic**, **teratogenic**, and potentially **carcinogenic**. It should not be used in pregnancy. Adequate contraception should be used by both sexes during vincristine treatment and for at least 6 months after the last dose. **Breast feeding** is not recommended since it is unknown whether vincristine or its metabolites are secreted in milk. **Fertility** may be affected.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Asparaginase	↑ neuropathy; disturbances of erythropoiesis	asparaginase may ↓ hepatic clearance of vincristine	give vincristine 12-24 hours before asparaginase
Digoxin, ciprofloxacin	↓ effect of digoxin, ciprofloxacin	↓ absorption	Caution; monitor.
Mitomycin	Acute bronchopasm has reported to occur minutes to hours after administration with vinca alkaloids	Unknown	Caution
nifedipine	↑ half-life of vincristine	possibly decreased excretion of vincristine	Avoid combination; monitor closely if given concurrently
phenytoin	↓ serum concentrations of phenytoin	↓ absorption or increased metabolism	monitor serum levels of phenytoin and adjust dose prn

verapamil	↑ vincristine toxicity	↓ protein binding	Avoid combination; monitor closely if given concurrently
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ vincristine effect	↑ metabolism	Caution
Potent CYP 3A4 inhibitors (erythromycin, INH, itraconazole)	↑ vincristine toxicity, especially neurotoxicity	↓ metabolism	Caution
Ototoxic drugs (e.g. cisplatin, aminoglycosides)	↑ ototoxicity risk	Additive; hearing impairment (8th cranial nerve damage) have been described in patients receiving vinca alkaloids	Use with extreme caution

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests; baseline and regular	At each visit
CBC and electrolytes; baseline and regular	
Clinical assessment of neurotoxicity, local toxicity, tumour lysis syndrome	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

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